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Which Subgroup of Patients With Dilated Cardiomyopathy Would Benefit From Long-Term Beta-Blocker Therapy? A Histologic Viewpoint

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Objectives. The purpose of this study was to elucidate whether the effectiveness of long-term beta-blocker therapy could be predicted before this therapy is started.

Background. Long-term beta-blocker therapy has recently been reported to provide a favorable effect in treatment of congestive heart failure due to dilated cardiomyopathy.

Methods. Several measurements including histologic variables before administration of metoprolol were retrospectively compared among 18 good responders (showing improvement of at least one New York Heart Association functional class or an increase in ejection fraction ≥0.10 12 months after drug administration) and 12 poor responders without such improvement.

Results. Although there were no significant differences between the two groups in age, gender, functional class, heart rate, blood pressure, pulmonary capillary wedge pressure, cardiac index, left ventricular end-diastolic dimension and ejection fraction, percent fibrosis estimated by the point-counting method in endomyocardial biopsy specimens was significantly lower in good than in poor responders (7.6 ± 5.7 vs. 14.2 ± 9.7%, $p < 0.05$). Moreover, when the types of fibrosis were classified as interfascicular and intercellular by the dominance of counted points, there were 13 cases of interfascicular fibrosis and 5 cases of intercellular fibrosis in good responders and 1 case of interfascicular fibrosis and 11 cases of intercellular fibrosis in poor responders ($p < 0.001$, sensitivity 72%, specificity 91%, predictive accuracy 80%). These results suggest that improvement with long-term beta-blocker therapy may be more likely to occur in patients with less myocardial fibrosis, with interfascicular fibrosis the dominant type.

Conclusions. The extent and type of fibrosis may be important factors in the prediction of the effectiveness of long-term beta-blocker therapy for dilated cardiomyopathy.

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Dilated cardiomyopathy is a heart muscle disease characterized by left ventricular dilation and impaired contraction of unknown cause, resulting in a poor prognosis. Several investigators (1–11) recently reported that long-term beta-blocker therapy could provide a favorable effect in treatment of congestive heart failure due to dilated cardiomyopathy. In these studies, it was shown that long-term beta-blocker therapy improved New York Heart Association functional class, exercise capacity (1,2), hemodynamic state (3–6) and survival rate (7–9), and that withdrawal of beta-blocking agents produced a deleterious effect (10,11). These results revealed the usefulness of long-term beta-blocker therapy in patients with dilated cardiomyopathy. However, there was a subgroup of patients with dilated cardiomyopathy who did not respond to the beta-blocker therapy (9,11). It remains unclear which subgroup of patients with dilated cardiomyopathy would be likely to benefit from long-term beta-blocker therapy.

The purpose of this study was to elucidate whether the effectiveness of long-term beta-blockade could be predicted from a variety of data, including histologic findings, before this therapy was begun in patients with dilated cardiomyopathy.

Methods

Patient selection. The study group consisted of 30 patients with dilated cardiomyopathy who experienced at least one episode of decompensated heart failure. These 30 patients of a consecutive series of 63 patients with dilated cardiomyopathy in our previous randomized controlled study (4,5,12) had been followed up as the group with the administration of a beta-blocker. Dilated cardiomyopathy was diagnosed by echocardiography, coronary angiography and endomyocardial biopsy, according to the criteria proposed by the World Health Organization/International Society and Federation of Cardiology Task Force (13). No

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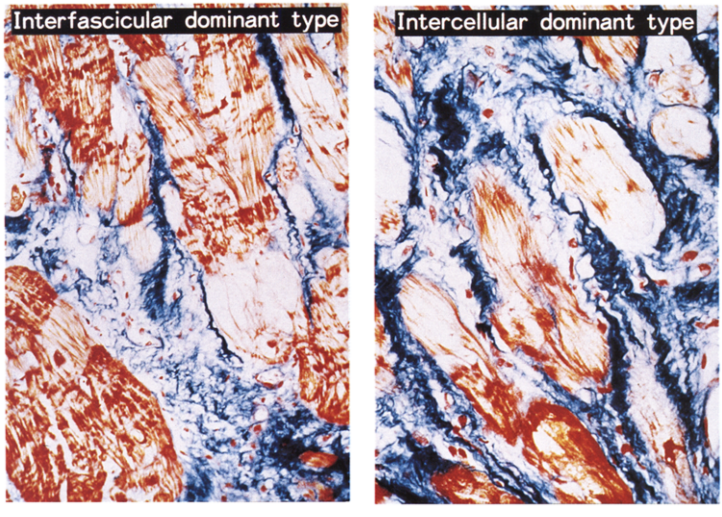

Figure 1. Representative types of fibrosis in patients with dilated cardiomyopathy. **Left,** Dominant interfascicular type of fibrosis in which the fibrous tissue is relatively localized and more fibrous tissue lies in the interfascicular space than the intercellular space. **Right,** Dominant intercellular type of fibrosis in which the diffuse fibrous tissue mainly encircles and separates individual muscle fibers.

patient had coronary artery disease (>25% diameter reduction of a major coronary vessel). Of the 30 study patients, 10 had minor arteriosclerosis with ≤25% lumen stenosis. In all patients, acute or chronic myocarditis was excluded by the finding at endomyocardial biopsy. Other causes of cardiomyopathy were also excluded. Subjects were enrolled during the stable stage of the disease after conventional treatment with digitalis and diuretic drugs for ≥1 month. The mean age of the patients was 58 years (range 21 to 72); there were 19 men and 11 women. The mean interval from the onset of symptoms to enrollment was 31 months (range 2 to 120).

Measurements before the administration of a beta-blocking agent. Before the administration of a beta-blocking agent, all patients underwent echocardiography, cardiac catheterization and left ventricular endomyocardial biopsy.

Echocardiography. Two-dimensional echocardiography was performed with a Toshiba SSH-65A or 160A recorder equipped with 2.5- or 3.75-MHz transducer. The standard technique (14) was employed for sizing the left ventricle. Left ventricular dimensions were measured at end-diastole on the R wave of the electrocardiogram (ECG)-derived QRS complex and at end-systole just below the level of the mitral leaflets through the standard left parasternal window. The transducer position was aided by the cross-sectional echocardiographic analysis. Left ventricular ejection fraction was calculated by the method of Gibson (15).

Cardiac catheterization. A Swan-Ganz thermodilution catheter was introduced through the right subclavian vein and positioned in the pulmonary artery. Heart rate, systemic blood pressure and pulmonary wedge pressure were measured. Cardiac output was determined by the thermodilution technique.

Endomyocardial biopsy. In each patient, at least three endomyocardial biopsy samples were taken from the free wall of the left ventricle, using an Olympus bioptome and a 6F long sheath inserted from femoral artery into left ventricle. The average weight of the specimens was 2.72 ± 0.24 mg. All samples were used for point counting according to the method of Weibel et al. (16) after Azan-Mallory staining. Cross points falling on fibrosis, excluding endocardial fibrosis, as well as that on myocytes in the magnified picture (×40), were counted by two independent microscopists who had no knowledge of clinical data. The total count was 882 ± 140 in each patient. The volume fraction of fibrous tissue was obtained as percent fibrosis, which was calculated by dividing the count of cross points falling on fibrosis by the total count. Furthermore, the dominant type of fibrosis was classified as intercellular or interfascicular by

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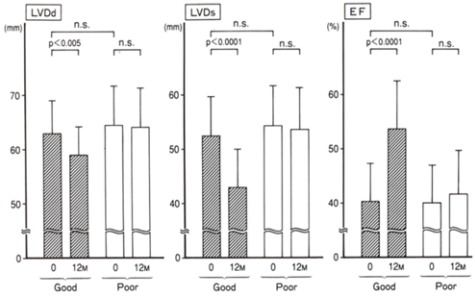

Figure 2. Echocardiographic changes in good and poor responders with dilated cardiomyopathy to long-term beta-blocker therapy. Data are mean values ± SD. Good responders (hatched bars) had improvement of at least one New York Heart Association functional class or an increase in ejection fraction ≥0.10, whereas none of the poor responders (open bars) had such improvement. Note that there were no significant differences in ejection fraction (EF), left ventricular end-diastolic dimension (LVDd) or left ventricular end-systolic dimension (LVDs) between good and poor responders before the start of beta-blocker therapy.

the dominancy of the counted points of each fibrosis. Intercellular and interfascicular fibrous tissues were determined respectively, according to the report of Anderson et al. (17) on histopathologic types of myocardial fibrosis (Fig. 1). Intercellular fibrous tissue encircled and separated individual fibers so that every muscle fiber in the affected area would be ensheathed. In contrast, interfascicular fibrous tissue was associated with collagenous tissue to the adventitia of peripheral vessels. These vessels lay between groups of myocardial fibers so that interfascicular fibrous tissue delineated groups of muscle fibers into bundles or fascicles.

Drug protocol. Metoprolol was administered at an initial dose of 5 to 10 mg/day. The dose was increased in stepwise increments by 5 to 20 mg/day over an interval of 2 to 8 weeks, taking care of deterioration of heart failure up to the therapeutic final dose of 60 mg/day unless severe hypotension (<80 mm Hg), bradycardia (<40 beats/min) or any signs of clinical decompensation appeared. During the follow-up period, the dose of other drugs for heart failure remained unchanged and neither angiotensin-converting enzyme inhibitors or calcium channel antagonists were administered.

Evaluation of the effectiveness of long-term beta-blocker therapy. The effectiveness of long-term beta-blocker therapy was assessed again by echocardiography 12 months after the administration of metoprolol, because improvement was shown to be a slow process that takes from 3 to 12 months in our and other previous studies (4,5,11). According to the degree of improvement in functional class and left ventricular ejection fraction, patients were classified into two groups: good responders with improvement of at least one functional class or increase in ejection fraction of ≥0.10 and poor responders without such improvement with long-term beta-blocker therapy.

Statistical analysis. Results were expressed as mean value ± SD. A two-factor repeated measures analysis of variance was used for paired data (comparison of echocardiographic data between before and 12 months after beta-blocker therapy) and unpaired data (comparisons between good and poor responders). The relation between the response to long-term beta-blocker therapy and the dominant type of fibrosis was examined with a chi-square test. A p value < 0.05 was considered significant.

Results

Response to long-term beta-blocker therapy. No patients showed deterioration of congestive heart failure as a result of metoprolol administration. Fourteen patients had both symptomatic and objective improvement. In contrast, the other 12 patients had neither symptomatic nor objective improvement. The remaining four patients had improvement of one functional class without an increase in ejection fraction ≥0.10. Accordingly, 18 of 30 patients with dilated cardiomyopathy had a good response to long-term beta-blocker therapy, whereas the remaining 12 patients had a poor response. All but three patients received the final therapeutic dose of 60 mg/day of metoprolol. These three patients (one good responder and two poor responders) received a dose of 40 mg/day. There was no significant difference in the final dose of metoprolol between good and poor responders. Figure 2 shows echocardiographic changes 12 months after the start of beta-blocker therapy in good and poor responders. In good responders, left ventricular end-diastolic (62.7 ± 6.1 to 59.3 ± 5.5 mm, $p < 0.005$) and end-systolic (52.5 ± 7.1 to 43.0 ± 7.1 mm, $p < 0.0001$) dimensions significantly decreased and ejection fraction markedly increased (0.408 ± 0.067 to 0.538 ± 0.087, $p < 0.0001$). Conversely, in poor responders, there were no significant changes in left ventricular dimension or ejection fraction.

Comparison of baseline data in good and poor responders (Table 1). There were no significant differences between good and poor responders at entry in terms of the following: age, gender, functional class, hemodynamic variables such as heart rate, systemic blood pressure, pulmonary capillary wedge pressure, cardiac index and left ventricular end-diastolic, end-systolic dimensions and ejection fraction (Fig. 2).

Table 1. Baseline Data at Study Entry From Good and Poor Responders to Long-Term Beta-Blocker Therapy

	Good Responders (n = 18)	Poor Responders (n = 12)
Age (yr)	57.7 ± 11.3	58.0 ± 10.6
Gender (M/F)	11/7	8/4
NYHA functional class	2.8 ± 0.5	2.7 ± 0.4
Heart rate (beats/min)	93.0 ± 19.3	82.3 ± 20.3
SBP (mm Hg)	132.0 ± 21.4	130.0 ± 16.2
DBP (mm Hg)	82.7 ± 18.6	80.0 ± 14.3
PCWP (mm Hg)	12.6 ± 7.5	14.0 ± 5.4
CI (liters/min per m^2)	2.53 ± 0.65	2.52 ± 0.67

p = NS for all data. Data are expressed as mean value ± SD or number of patients. CI = cardiac index; DBP = systemic diastolic blood pressure; F = female; M = male; NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure; SBP = systemic systolic blood pressure.

Comparison of histologic findings in good and poor responders (Table 2). Percent fibrosis in good responders was significantly lower than that in poor responders (7.6 ± 5.7% vs. 14.2 ± 9.7%, $p < 0.05$). Table 2 shows the relation between the dominant fibrosis type and the effectiveness of long-term beta-blocker therapy. Thirteen of 18 good responders had dominant interfascicular fibrosis and 11 of 12 poor responders had dominant intercellular fibrosis. A significant relation was observed between the fibrosis type and the effectiveness of beta-blocker therapy (chi-square = 11.8, $p < 0.001$). This fibrosis type gave a sensitivity of 72%, a specificity of 91% and a predictive accuracy of 80% for prediction of the effectiveness of long-term beta-blocker therapy.

Discussion

The present study demonstrated that long-term beta-blocker therapy would be expected to be more effective in patients with less myocardial fibrosis, with the dominant type of fibrosis being interfascicular rather than intercellular fibrosis. These results indicate that the extent and type of fibrosis in endomyocardial biopsy specimens might be important factors for predicting the effectiveness of long-term beta-blocker therapy.

It has been reported (1,2,8,9,11) that a subgroup of patients with dilated cardiomyopathy responded dramatically to long-term beta-blocker therapy, with symptomatic and functional improvement and prolonged life. Therefore, it is important to identify the characteristics that distinguish those patients who will benefit from long-term beta-blocker therapy from those whom it will not benefit.

Table 2. Relation Between the Dominant Type of Myocardial Fibrosis and the Response to Beta-Blocker Therapy in Patients With Dilated Cardiomyopathy

Response to Beta-Blocker Therapy	Dominant Type of Fibrosis		All Patients
	Interfascicular	Intercellular	
Good responders	13	5	18
Poor responders	1	11	12
All patients	14	16	30

$p < 0.001$, chi-square = 11.8 for all values. Data are expressed as number of patients.

Identification of good responders to long-term beta-blocker therapy. Some investigators (1,2,18) reported that the most favorable response occurs in patients with a higher heart rate at rest and more advanced left ventricular dysfunction. However, in the present study, heart rate, blood pressure, pulmonary capillary wedge pressure, cardiac index or echocardiographic variables of cardiac function did not help predict improvement with long-term beta-blocker therapy. It was also reported (19) that hemodynamic variables before the administration of a beta-blocker did not predict the clinical response to the drug. Thus, the clinical significance of hemodynamic variables for predicting the effectiveness of beta-blocker therapy remains controversial in patients with dilated cardiomyopathy.

It was reported (18) that the tolerance to beta-blockers in dilated cardiomyopathy might be at least partially predicted by the severity of structural abnormality, which was qualitatively estimated from the extent of fibrosis, myocyte hypertrophy and nuclear abnormality in endomyocardial biopsy samples. In that study (18), it was shown that there was a 50% chance of deterioration in the presence of the most severe histologic change, whereas most patients with mild or moderate abnormalities should tolerate beta-blocker therapy. Thus, only tolerance to beta-blocker therapy was discussed in their study (18). In the present study, we demonstrated that histologic findings such as the dominant type and extent of fibrosis might be important factors for predicting the effectiveness of long-term beta-blocker therapy in patients who are able to tolerate the drug.

Although good responders in this study actually had significantly less myocardial fibrosis than that of poor responders, some patients with a similar extent of fibrosis showed various responses to long-term beta-blockade. It is suggested that the extent of fibrosis might not be the only variable that explains the difference in the response to long-term beta-blocker therapy. Conversely, it might be thought that histologic findings themselves have already determined the subsequent clinical course in patients with dilated cardiomyopathy, irrespective of the administration of a beta-blocker. However, in our previous studies (4,5), there was no significant clinical improvement 12 months after enrollment in patients without long-term beta-blockade, irrespective of the dominant type of fibrosis (intercellular dominant type: left ventricular end-diastolic dimension 65.5 ± 12.2 to 66 ± 12.3 mm, ejection fraction 0.435 ± 0.055 to 0.45 ± 0.11 [n = 6]; interfascicular dominant type: left ventricular end-diastolic dimension 62.7 ± 3.4 to 59.4 ± 5.9 mm, ejection fraction 0.404 ± 0.077 to 0.454 ± 0.119 [n = 7]). Therefore, it is natural to consider that clinical improvement in this study was attributed to the administration of metoprolol and that histologic findings such as the

extent and type of fibrosis could determine the response to long-term beta-blocker therapy in patients with dilated cardiomyopathy.

Other factors that might affect the response to beta-blocker therapy. The interval from the onset of symptoms to enrollment in this study did not correlate with the extent of fibrosis ($r = 0.102$). Furthermore, there was no significant difference in this interval between patients with dominance of interfascicular or intercellular fibrosis (30.3 ± 31.2 vs. 32.5 ± 31.7 months). Thus, neither the extent nor the type of fibrosis was related to this time difference. However, this interval tended to be shorter in good responders than in poor responders (23.2 ± 18.2 to 39.3 ± 34.4 months). Therefore, it is suggested that the earlier therapy is begun, the more effective it would be in patients with dilated cardiomyopathy.

We also performed symptom-limited multistage supine bicycle ergometry, monitoring the hemodynamic variables with a Swan-Ganz catheter in 12 study patients. Although there was no difference between good and poor responders in pulmonary capillary wedge pressure at the end point of the exercise test after long-term beta-blockade (good responders, 28.3 ± 14.2 to 29.4 ± 11.7 [n = 7]; poor responders, 24.6 ± 11.4 to 25.4 ± 5.6 mm Hg [n = 5]), cardiac index tended to increase in good responders (5.12 ± 1.19 to 5.39 ± 1.91 liters/min per m^2), whereas that in poor responders tended to decrease (5.58 ± 1.88 to 5.27 ± 1.98 liters/min per m^2). Furthermore, stroke work index at the end of exercise tended to increase in good responders after long-term beta-blockade (48.5 ± 19.5 to 59.1 ± 18.7 mm Hg·ml/m^2, $p = 0.07$), while that in poor responders tended to decrease (74.3 ± 41.0 to 64.6 ± 28.5 mm Hg·ml/m^2). The percent improvement in stroke work index was significantly better in good responders than in poor responders (32.6 ± 35.2 vs. −7.72 ± 18.3%, $p < 0.05$). It is suggested that these exercise test data support the reasonableness of clinical improvement with long-term beta-blockade.

Relation between myocardial fibrosis and left ventricular function. Although there was a considerable difference in the extent and type of myocardial fibrosis between good and poor responders in this study, there was no difference in the degree of left ventricular functional impairment before the initiation of beta-blocker therapy. The finding that there was no significant correlation between the extent of fibrosis and left ventricular dysfunction in patients with dilated cardiomyopathy was similar to that in reports in previous endomyocardial biopsy studies (20,21). However, this was not the case in other reports (22,23). Thus, the relation between myocardial fibrosis and left ventricular dysfunction remains controversial.

Catecholamine hypothesis: pathophysiologic consideration of the types of fibrosis. Plasma catecholamine level is known as a major predictive factor of death in patients with heart failure (24). It has been reported (25) that a compensatory increase in sympathetic nerve activity for the failing heart will lead to worsening of the failing status by means of beta-receptor down regulation and catecholamine-induced cardiac toxicity. In the present study, the plasma concentration of norepinephrine before beta-blocker therapy tended to be higher in good than in poor responders (0.66 ± 0.29 [n = 10] vs. 0.49 ± 0.38 ng/ml [n = 7]), whereas there was no significant difference in beta-receptor density of peripheral lymphocytes (1,550 ± 980 [n = 9] vs. 1,409 ± 343 sites/cell [n = 5]) between the two groups. It is suggested that variables that characterize the adrenergic state might possibly be useful as a guide to beta-blocker therapy in dilated cardiomyopathy.

The pathogenesis of interfascicular and intercellular fibrosis remains unknown, although it is reasonable that the more extensive the fibrosis, the less the improvement in cardiac function in terms of quantity of residual cell volume. In the present study, however, plasma concentration of norepinephrine in patients with dominant interfascicular fibrosis tended to be higher than in those with dominant intercellular fibrosis (0.61 ± 0.28 [n = 9] vs. 0.51 ± 0.38 ng/ml [n = 8]). It is suggested that the fibrosis type might possibly be related to the catecholamine level.

Limitations of this study. Because myocardial fibrosis was quantified with the point-counting method in biopsy samples, there were some inherent limitations in the biopsy study. In terms of the reproducibility of measurements by the point-counting method, the interobserver variability for percent fibrosis was small in this study (4.5 ± 2%, n = 6). In addition, the determination of the dominant fibrosis type did not depend on observers. Another inherent limitation was representativeness of the whole myocardium in endomyocardial biopsy samples. The morphologic changes in the myocardium were more or less uniformly distributed over the entire myocardium in patients with dilated cardiomyopathy (23,26), although there might be some focal processes that could affect our quantitative analysis. However, it is evident that the effectiveness of long-term beta-blocker therapy could be related to the myocardial fibrosis content in patients with dilated cardiomyopathy despite these limitations. In addition, this is a retrospective study. Accordingly, another prospective trial using an external sample will be needed to verify our results.

Conclusions. This study showed that the effectiveness of long-term beta-blocker therapy in patients with dilated cardiomyopathy can be predicted from the histologic findings such as the severity and the dominant type of fibrosis in endomyocardial biopsy specimens.

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